

Applicants: Virginia W. Cornish
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In the Claims

Please amend the claims pursuant to the provisions of proposed new rule 121 as described in the Official Gazette on February 25, 2003, as follows:

b2 91. (currently amended) A compound comprising a small-molecule portion to be tested for binding to a receptor having the formula:

H1-Y-H2

wherein H1 is methorexate methotrexate (Mtx) or an analog thereof that binds in a cell to dihydrofolate reductase (DHFR);

wherein H2 is capable of the small-molecule portion of the compound to be tested for binding to a receptor, and

wherein Y is a moiety providing a covalent linkage between H1 and H2, which may be present or absent, and when absent, H1 is covalently linked to H2.

92. (currently amended) The compound of claim 91, wherein H2 is dexamethasone (Dex) or an analog thereof.

93. (currently amended) The compound of claim 91, wherein H1 is Mtx and H2 is Dex or an analog thereof.

94. The compound of claim 91, having the formula:

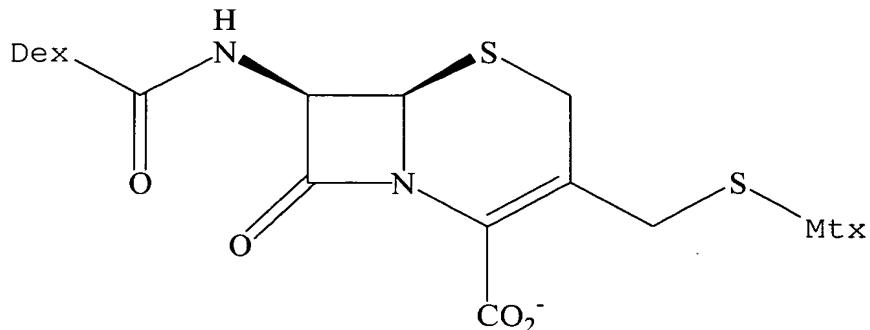
Mtx-Y-H2.

95. The compound of claim 91, having the formula:

Dex-Y-Mtx.

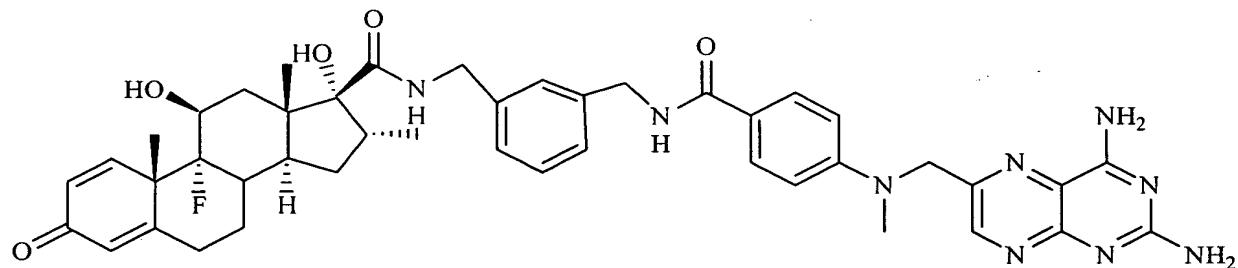
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96. The compound of claim 95, having the formula:

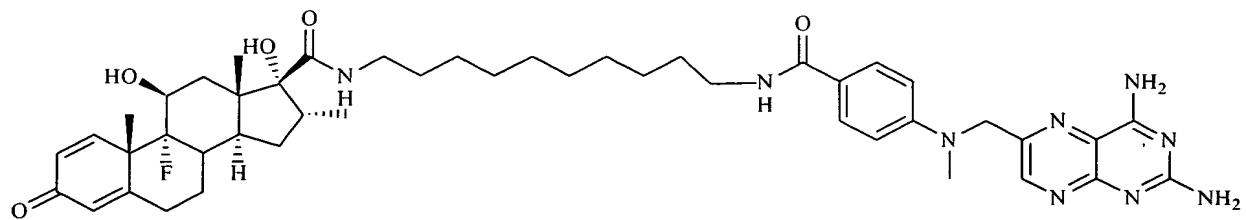


97-105 (Canceled).

106. The compound of claim 95 having the formula:

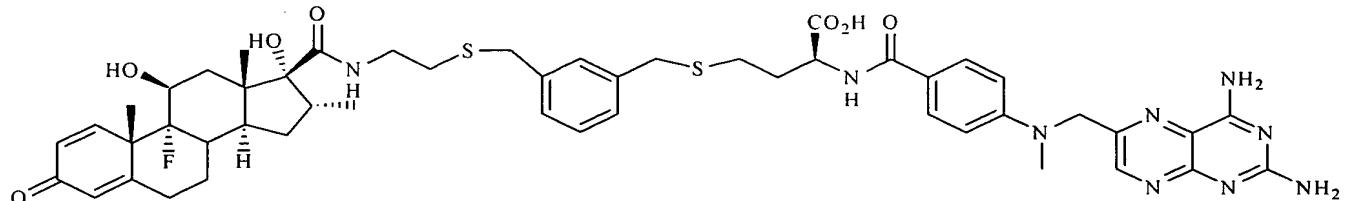


107. The compound of claim 95 having the formula:



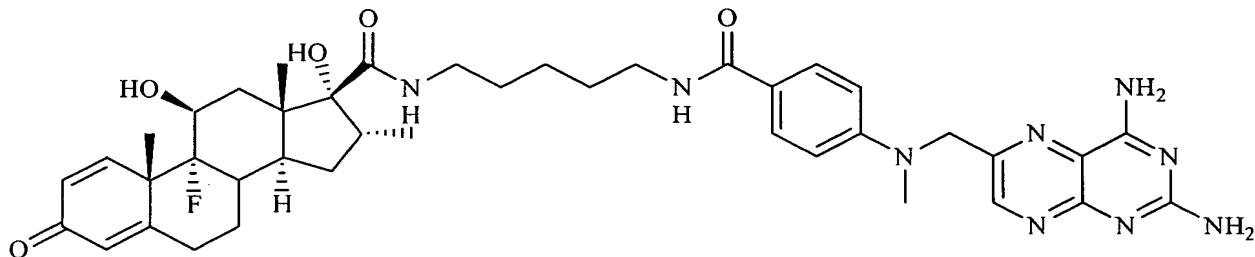
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108. The compound of claim 95 having the formula:

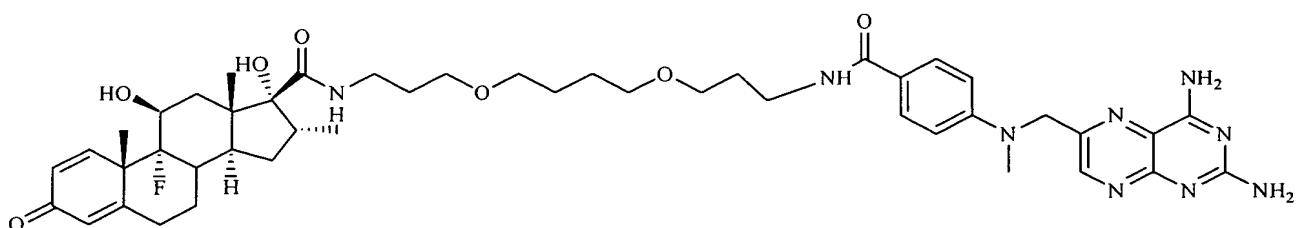


B2

109. The compound of claim 95 having the formula:



110. The compound of claim 95, having the formula:



111. (currently amended) A complex between ~~the compound of claim 91~~

i) a compound comprising a portion to be tested for binding to a receptor having the formula H₁-Y-H₂,

wherein H₁ is methotrexate (Mtx) or an analog thereof that binds in a cell to dihydrofolate

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reductase (DHFR);

wherein H2 is the portion of the compound to be tested for binding to a receptor; and

wherein Y is a moiety providing a covalent linkage between H1 and H2, which may be present or absent, and when absent, H1 is covalently linked to H2, and

ii) a fusion protein which comprises a binding domain capable of binding to methotrexate, wherein that binds to H1 of the compound binds to the binding domain of the fusion protein.

112. The complex of claim 111, wherein the binding domain is that of the dihydrofolate reductase (DHFR).

113-118 (Canceled).

119. The complex of claim 111, wherein the fusion protein is DHFR-(DNA-binding domain).

120. The complex of claim 111, wherein the fusion protein is DHFR-LexA.

121. The complex of claim 111, wherein the fusion protein is DHFR-(transcription activation domain).

122. The complex of claim 111, wherein the fusion protein is DHFR-B42.

123. A complex between the compound of any one of claims of claims 106-110, and the fusion protein DHFR-LexA.

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124. The complex between the compound of any one of claims of claims 106-110, and the fusion protein DHFR-B42.
125. A cell comprising the complex of claim 111.
126. The cell of claim 125, where the cell is selected from the group consisting of yeast, bacteria or mammalian.
127. (currently amended) The cell of claim 125, where the cell is selected from the group consisting of *S. cerevisiae*, and *E. coli*.
128. (Withdrawn) A method of dimerizing two fusion proteins inside a cell using the compound of claim 91, comprising the steps of a) providing a cell that expresses a first fusion protein which comprises a binding domain that binds to H1 and second fusion protein which comprises a binding domain that binds to H2, and b) contacting the compound of claim 91 with the cell so as to dimerize the two fusion proteins.
129. (Withdrawn) The method of claim 128, wherein the first fusion protein or the second fusion protein is DHFR-(DNA-binding domain).
130. (Withdrawn) The method of claim 128, wherein the first fusion protein or the second fusion protein is DHFR-LexA.

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131. (Withdrawn) The method of claim 128, wherein the first fusion protein or the second fusion protein is DHFR-(transcription activation domain).

132. (Withdrawn) The method of claim 128, wherein the first fusion protein or the second fusion protein is DHFR-B42.

133. (Withdrawn) A method for identifying a molecule that binds a known target in a cell from a pool of candidate molecules, comprising:

(a) covalently bonding each molecule in the pool of candidate molecules to a methotrexate moiety or an analog of methotrexate to form a screening molecule;

(b) introducing the screening molecule into a cell which expresses a first fusion protein comprising a binding domain capable of binding methotrexate, a second fusion protein comprising the known target, and a reporter gene wherein expression of the reporter gene is conditioned on the proximity of the first fusion protein to the second fusion protein;

(c) permitting the screening molecule to bind to the first fusion protein and to the second fusion protein so as to activate the expression of the reporter gene;

(d) selecting which cell expresses the reporter gene; and

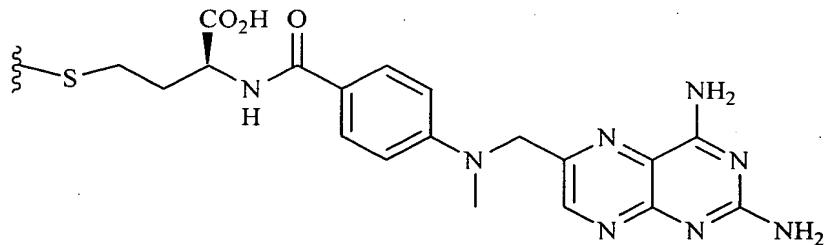
(e) identifying the small molecule that binds the known target.

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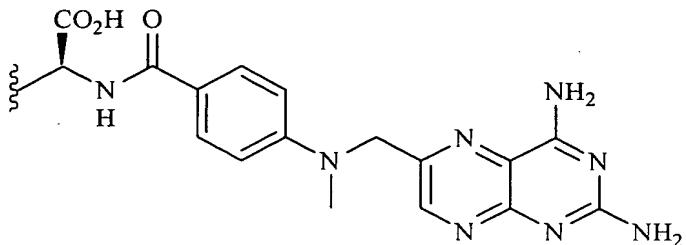
141. (New) The compound of claim 91, wherein H2 is a moiety selected from the group consisting of steroids, hormones, cofactors, antibiotics, sugars, or enzyme inhibitors.

142. (New) The complex of claim 111, wherein in the compound, H2 is a moiety selected from the group consisting of steroids, hormones, cofactors, antibiotics, sugars, or enzyme inhibitors.

143. The compound of claim 91, wherein H1 has the formula:

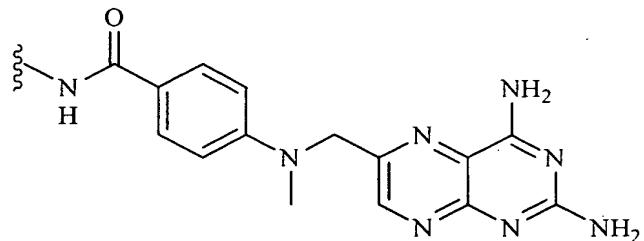


144. The compound of claim 91, wherein H1 has the formula:

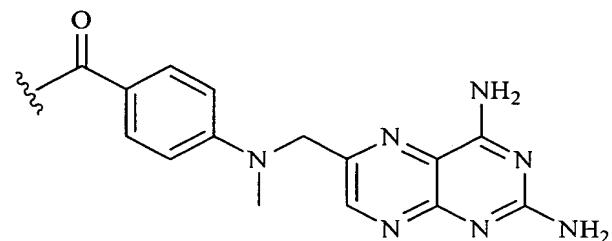


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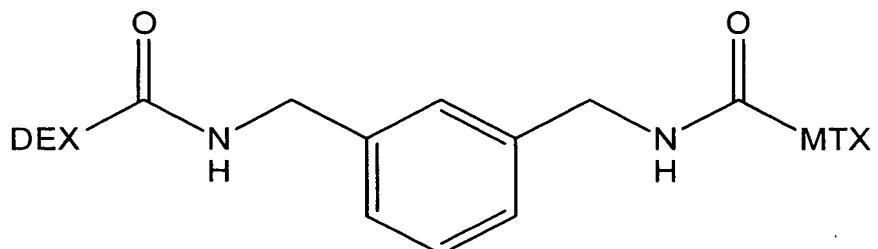
145. The compound of claim 91, wherein H1 has the formula:



146. The compound of claim 91, wherein H1 has the formula:

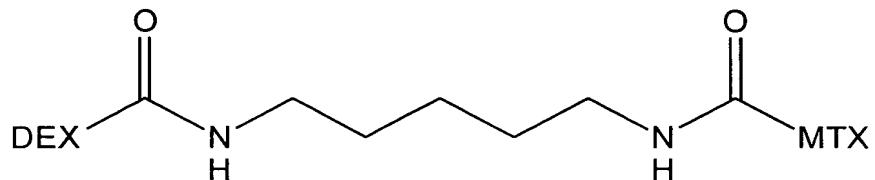


147. The compound of claim 95 having the formula:

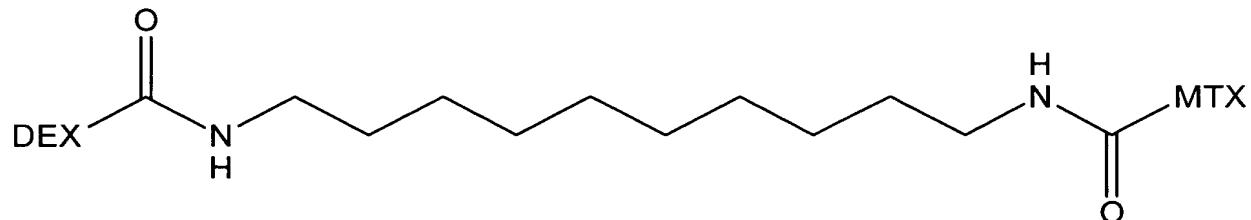


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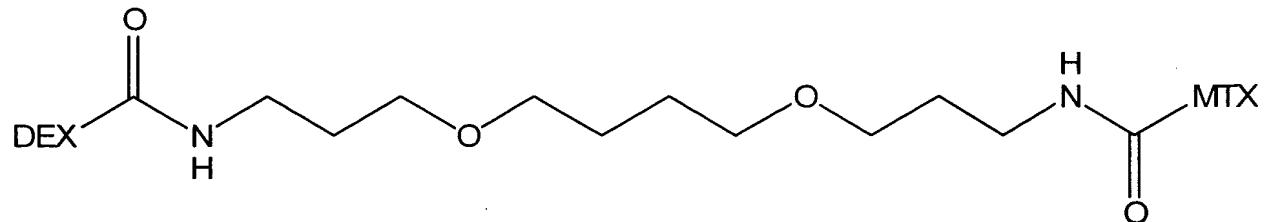
148. The compound of claim 95 having the formula:



149. The compound of claim 95 having the formula:



150. The compound of claim 95 having the formula:



151. (New) A yeast three-hybrid system comprising
a compound of the formula H1-Y-H2 having a portion which
is to be tested for binding to a receptor,
wherein H1 is methotrexate (Mtx) or an analog
thereof that binds in a cell to dihydrofolate

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reductase (DHFR);

wherein H2 is the portion of the compound to be tested for binding to a receptor; and

wherein Y is a moiety providing a covalent linkage between H1 and H2, which may be present or absent, and when absent, H1 is covalently linked to H2.

152. (New) A yeast three-hybrid system comprising a complex between

i) a compound of the formula H1-Y-H2 having a portion which is to be tested for binding to a receptor,

wherein H1 is methotrexate (Mtx) or an analog thereof that binds in a cell to dihydrofolate reductase (DHFR);

wherein H2 is the portion of the compound to be tested for binding to a receptor; and

wherein Y is a moiety providing a covalent linkage between H1 and H2, which may be present or absent, and when absent, H1 is covalently linked to H2, and

ii) a fusion protein which comprises a binding domain that binds to H1 of the compound.

153. (New) A method for identifying a protein target to which a molecule having a known biological function binds, comprising:

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(a) providing a screening molecule having the formula H1-Y-H2,

wherein H1 is methotrexate (Mtx) or an analog thereof that binds in a cell to dihydrofolate reductase (DHFR);

wherein H2 is the molecule having a known biological function; and

wherein Y is a moiety providing a covalent linkage between H1 and H2, which may be present or absent, and when absent, H1 is covalently linked to H2,

(b) introducing the screening molecule into a cell which expresses a first fusion protein comprising a binding domain capable of binding methotrexate, a second fusion protein comprising the protein target to be identified, and a reporter gene wherein expression of the reporter gene is conditioned on the proximity of the first fusion protein to the second fusion protein;

(c) permitting the screening molecule to bind to the first fusion protein and to the second fusion protein so as to activate the expression of the reporter gene;

(d) selecting which cell expresses the reporter gene; and

(e) identifying the protein target.

154. (New) The method of claim 154, wherein the protein target to be identified is encoded by a DNA from the group consisting of genomicDNA, cDNA and syntheticDNA.